

U.S.S.N: 10/027,982

Response to Advisory Action dated September 2, 2003

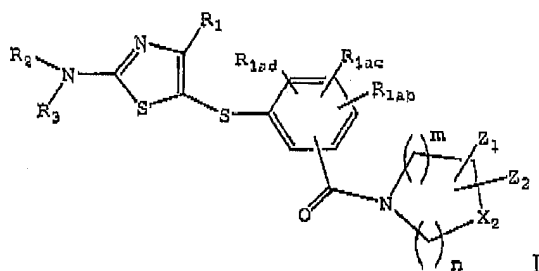
**Amendments to the Claims:**

This listing of claims will replace all prior versions, and listings, of claims in the application:

**Listing of Claims:**

Claims 1-6 (Canceled).

Claim 7 (Currently amended). A compound of formula I



diastereomers, enantiomers or salts thereof

where

R<sub>1</sub> is hydrogen or R<sub>6</sub>;

R<sub>1ab</sub> and R<sub>1ac</sub> are independently hydrogen, R<sub>6</sub> or -OR<sub>6</sub>;

R<sub>1ad</sub> is hydrogen;

one of R<sub>2</sub> or R<sub>3</sub> is hydrogen or alkyl and the other R<sub>2</sub> or R<sub>3</sub> is -Z<sub>4</sub>-R<sub>6a</sub>, where: Z<sub>4</sub> is -Z<sub>11</sub>-C(O)-Z<sub>12</sub>-  
and R<sub>6a</sub> is phenyl substituted with Z<sub>3</sub>;

R<sub>6</sub> is alkyl;

R<sub>1</sub>, R<sub>1ab</sub>, R<sub>1ac</sub> and R<sub>1ad</sub> are independently

(1) — hydrogen or R<sub>6</sub>;

(2) — OH or -OR<sub>6</sub>;

(3) — SH or -SR<sub>6</sub>;

(4) — C(O)<sub>q</sub>H, C(O)<sub>q</sub>R<sub>6</sub>, or -C(O)<sub>q</sub>R<sub>6</sub>, where q is 1 or 2;

(5) — SO<sub>3</sub>H or -S(O)<sub>q</sub>R<sub>6</sub>;

U.S.S.N: 10/027,982

Response to Advisory Action dated September 2, 2003

(6) —halo;

(7) —cyano;

(8) —nitro;

(9) — $Z_4-NR_7R_8$ ;(10) — $Z_4-N(R_9)-Z_5-NR_{10}R_{11}$ ;(11) — $Z_4-N(R_{12})-Z_5-R_6$ , or(12) — $P(O)(OR_6)_2$ ; $R_2$  and  $R_3$  are each independently H,  $Z_4-R_{6a}$ , or  $Z_4-NR_{7a}R_{8a}$ ; $R_6$ ,  $R_{6a}$ , and  $R_{6b}$  are independently alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aralkyl, heterocyclo, or heterocycloalkyl, each of which is unsubstituted or substituted with  $Z_1$ ,  $Z_2$  and one or more groups  $Z_3$ ; $R_7a$ ,  $R_{8a}$ ,  $R_9$ ,  $R_{10}$ ,  $R_{11}$  and  $R_{12}$ (1) are each independently hydrogen, or  $Z_4R_{6b}$ ; or(2)  $R_{7a}$  and  $R_{8a}$  may together be alkylene, alkenylene, or heteroalkylene, completing a 3- to 8-membered saturated or unsaturated ring with the nitrogen atom to which they are attached, which ring is unsubstituted or substituted with  $Z_1$ ,  $Z_2$  and one or more groups  $Z_3$ ; or(3) any two of  $R_9$ ,  $R_{10}$  and  $R_{11}$  may together be alkylene, alkenylene or heteroalkylene completing a 3- to 8-membered saturated or unsaturated ring together with the nitrogen atoms to which they are attached, which ring is unsubstituted or substituted with one or more  $Z_1$ ,  $Z_2$  and  $Z_3$ ; $X_2$  is  $CZ_{3a}$ ,  $NZ_{3a}$ , O or S; $Z_{3a}$  is  $-C(O)_qZ_{6a}$ , where q is 1 H, hydroxy, optionally substituted alkyl, optionally substituted heterocyclo, optionally substituted aryl, optionally substituted aralkyl,  $OZ_6$ ,  $C(O)_qH$ ,  $-C(O)_qZ_{6a}-Z_4-NZ_7Z_8$ , or  $Z_4-N(Z_{10})-Z_5-Z_6$ ;

n is 1 to 3 2;

m is zero to 2 1;

 $Z_1$  and  $Z_2$  are hydrogen; $Z_3$  is  $-Z_4-NZ_7Z_8$ , where  $Z_4$  is alkyl; $Z_1$ ,  $Z_2$  and  $Z_3$  are each independently(1) —hydrogen or  $Z_6$ ;

U.S.S.N: 10/027,982  
Response to Advisory Action dated September 2, 2003

- (2) ~~—OH or —OZ<sub>6</sub>;~~  
 (3) ~~—SH or —SZ<sub>6</sub>;~~  
 (4) ~~—C(O)<sub>q</sub>H<sub>3</sub>—C(O)<sub>q</sub>Z<sub>6</sub>, or —O—C(O)<sub>q</sub>Z<sub>6</sub>, where q is 1 or 2;~~  
 (5) ~~—SO<sub>2</sub>H, —S(O)<sub>q</sub>Z<sub>6</sub>, or S(O)<sub>q</sub>N(Z<sub>9</sub>)Z<sub>6</sub>;~~  
 (6) ~~—halo;~~  
 (7) ~~—cyano;~~  
 (8) ~~—nitro;~~  
 (9) ~~—Z<sub>4</sub>NZ<sub>7</sub>Z<sub>8</sub>;~~  
 (10) ~~—Z<sub>4</sub>N(Z<sub>9</sub>)Z<sub>5</sub>NZ<sub>7</sub>Z<sub>8</sub>;~~  
 (11) ~~—Z<sub>4</sub>N(Z<sub>10</sub>)Z<sub>5</sub>Z<sub>6</sub>;~~  
 (12) ~~—Z<sub>4</sub>N(Z<sub>10</sub>)Z<sub>5</sub>—H;~~  
 (13) ~~—oxo;~~  
 (14) ~~any two of Z<sub>4</sub>, Z<sub>2</sub>, and Z<sub>3</sub> on a given substituent may together be alkylene or alkenylene completing a 3 to 8 membered saturated or unsaturated ring together with the atoms to which they are attached; or~~  
 (15) ~~any two of Z<sub>4</sub>, Z<sub>2</sub>, and Z<sub>3</sub> on a given substituent may together be —O—(CH<sub>2</sub>)<sub>4</sub>—O;~~

Z<sub>4</sub> and Z<sub>5</sub> are each independently

- (1) ~~a single bond;~~  
 (2) ~~—Z<sub>11</sub>—S(O)<sub>q</sub>—Z<sub>12</sub>;~~  
 (3) ~~—Z<sub>11</sub>—C(O)—Z<sub>12</sub>;~~  
 (4) ~~—Z<sub>11</sub>—C(S)—Z<sub>12</sub>;~~  
 (5) ~~—Z<sub>11</sub>—O—Z<sub>12</sub>;~~  
 (6) ~~—Z<sub>11</sub>—S—Z<sub>12</sub>;~~  
 (7) ~~—Z<sub>11</sub>—O—C(O)—Z<sub>12</sub>;~~  
 (8) ~~—Z<sub>11</sub>—C(O)—O—Z<sub>12</sub>;~~ or  
 (9) ~~alkyl~~

Z<sub>6</sub> and Z<sub>6a</sub> is alkyl; are independently

- (i) ~~alkyl, hydroxyalkyl, alkoxyalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aralkyl, alkylaryl, cycloalkylaryl, heterocycle, or heterocycloalkyl;~~

U.S.S.N: 10/027,982

Response to Advisory Action dated September 2, 2003

(ii) ~~a group (i) which is itself substituted by one or more of the same or different groups (i);~~  
~~or~~

(iii) ~~a group (i) or (ii) which is independently substituted by one or more of the groups (2) to (15) of the definition of Z<sub>11</sub>;~~

Z<sub>7</sub> and Z<sub>8</sub> are each independently hydrogen or -Z<sub>4</sub>-Z<sub>6a</sub>, where Z<sub>4</sub> is a single bond;

Z<sub>7</sub>, Z<sub>8</sub>, Z<sub>9</sub> and Z<sub>10</sub>

~~(1) are each independently hydrogen or -Z<sub>4</sub>-Z<sub>6a</sub>;~~

~~(2) Z<sub>7</sub> and Z<sub>8</sub> may together be alkylene, alkenylene, or heteroalkylene completing a 3 to 8-membered saturated or unsaturated ring together with the atoms to which they are attached, which ring is unsubstituted or substituted with one or more Z<sub>1</sub>, Z<sub>2</sub> and Z<sub>3</sub>; or~~

~~(3) Z<sub>7</sub> or Z<sub>8</sub>, together with Z<sub>9</sub>, may be alkylene, alkenylene, or heteroalkylene completing a 3 to 8-membered saturated or unsaturated ring together with the nitrogen atoms to which they are attached, which ring is unsubstituted or substituted with one or more Z<sub>1</sub>, Z<sub>2</sub> and Z<sub>3</sub>;~~

Z<sub>11</sub> and Z<sub>12</sub> are each independently a single bond.

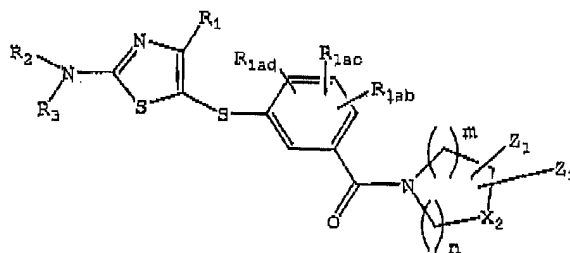
~~(1) a single bond,~~

~~(2) alkylene,~~

~~(3) alkenylene, or~~

~~(4) alkynylene;~~

Claim 8 (Previously presented). A compound of claim 7 having the formula



Claim 9 (Currently amended). A compound of claim 8 where

R<sub>2</sub> is hydrogen or alkyl; and

R<sub>3</sub> is -Z<sub>4</sub>R<sub>6a</sub>, where: Z<sub>4</sub> is -C(O)- and R<sub>6a</sub> is phenyl substituted with Z<sub>3</sub>.

U.S.S.N: 10/027,982

Response to Advisory Action dated September 2, 2003

~~(a)  $Z_4$  is a single bond and  $R_{6a}$  is heteroaryl optionally substituted with one or more  $Z_1$ ,  $Z_2$  or  $Z_3$ ;~~

~~(b)  $Z_4$  is  $C(O)$  and  $R_{6a}$  is~~

~~(1) aryl optionally substituted with one or more  $Z_1$ ,  $Z_2$  or  $Z_3$ ;~~

~~(2) alkyl optionally substituted with one or more  $Z_1$ ,  $Z_2$  or  $Z_3$ ;~~

~~(3) cycloalkyl optionally substituted with one or more  $Z_1$ ,  $Z_2$  or  $Z_3$ ; or~~

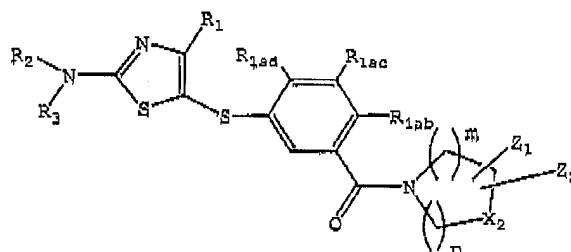
~~(4) heterocycle optionally substituted with one or more  $Z_1$ ,  $Z_2$  or  $Z_3$ ; or~~

~~(c)  $Z_4$  is  $C(O)O$  and  $R_{6a}$  is alkyl, cycloalkyl, aryl or aralkyl, any of which may be optionally substituted with one or more  $Z_1$ ,  $Z_2$  or  $Z_3$ .~~

Claim 10 (Currently amended). A compound of claim 9 wherein  $R_{1ab}$  [,] and  $R_{1ac}$  and  ~~$R_{1ad}$~~  are independently H [,] or alkyl, hydroxy, nitro, halo,  $OR_6$ ,  $NR_7R_8$ ,  $C(O)_qH$  or  $C(O)_qR_6$ .

Claim 11 (Original). A compound of claim 10 wherein  $R_{1ab}$  and  $R_{1ac}$  are independently alkyl.

Claim 12 (Currently amended). A compound of claim 8 having the following formula



where one of  $R_{1ab}$  [,] and  $R_{1ac}$  and  ~~$R_{1ad}$~~  is H and the other is alkyl or  $OR_6$  two are independently alkyl, hydroxy, nitro, halo,  $OR_6$ ,  $NR_7R_8$ ,  $C(O)_qH$  or  $C(O)_qR_6$ .

Claim 13 (Currently amended). A compound of claim 12 wherein one of  $R_{1ab}$  [,] and  $R_{1ac}$  and  ~~$R_{1ad}$~~  is H and the other is two are independently alkyl or  $OR_6$ .

Claim 14 (Previously presented). A compound of claim 13 wherein  $R_{1ac}$  is H.

U.S.S.N: 10/027,982  
Response to Advisory Action dated September 2, 2003

Claim 15 (Canceled).

Claim 16 (Canceled)

Claim 17 (Previously presented). A pharmaceutical composition comprising at least one compound of claim 7 and a pharmaceutically acceptable vehicle or carrier therefor.

Claim 18 (Original). A pharmaceutical composition of claim 17 further comprising at least one additional therapeutic agent selected from anti-inflammatory agents, anti-proliferative agents, anti-cancer agents or anti-cytotoxic agents.

Claim 19 (Original). A pharmaceutical composition of claim 18 wherein the additional therapeutic agents are selected from steroids, mycophenolate mofetil, LTD<sub>4</sub> inhibitors, CTLA4-Ig, LEA-29Y, phosphodiesterase inhibitors, antihistamines, or p<sup>38</sup> MAPK inhibitors.

Claim 20 (Withdrawn). A method of treating a Tec family tyrosine kinase-associated disorder comprising the step of administering to a patient in need thereof, an effective amount of at least one compound of claim 1.

Claim 21 (Withdrawn). The method of claim 20 wherein the Tec family tyrosine kinase-associated disorder is an Emt-associated disorder.

Claim 22 (Withdrawn). The method of claim 21 wherein the Emt-associated disorder is selected from transplant rejection, rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, lupus, graft vs. host disease, T-cell mediated hypersensitivity disease, psoriasis, Hashimoto's thyroiditis, Guillain-Barre syndrome, cancer, contact dermatitis, allergic disease, asthma, ischemic or reperfusion injury, atopic dermatitis, allergic rhinitis, or chronic obstructive pulmonary disease.

U.S.S.N: 10/027,982  
Response to Advisory Action dated September 2, 2003

Claim 23 (New). A method of treating a Tec family tyrosine kinase-associated disorder comprising the step of administering to a patient in need thereof, an effective amount of at least one compound of claim 7.

Claim 24 (New). The method of claim 23 wherein the Tec family tyrosine kinase-associated disorder is an Emt-associated disorder.

Claim 25 (New). The method of claim 24 wherein the Emt-associated disorder is selected from transplant rejection, rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, lupus, graft vs. host disease, T-cell mediated hypersensitivity disease, psoriasis, Hashimoto's thyroiditis, Guillain-Barre syndrome, cancer, contact dermatitis, allergic disease, asthma, ischemic or reperfusion injury, atopic dermatitis, allergic rhinitis, or chronic obstructive pulmonary disease.